predicted serum level at some appropriate time which will serve as a "check point" for the dosing plan. Significant deviation from the predicted level would indicate the need for further evaluation and possible revision of the dosage plan.

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HLA in Paternity Testing

HISTOCOMPATIBILITY ANTIGEN (HLA) typing now is recognized throughout the world as the single most discriminating test for determination of nonpaternity. Because of the large number of antigens involved in one genetic system of closely linked loci and the scattered distribution of these antigens in the population, the chance of exclusion with HLA typing alone is at least 91 percent and is 95 percent in combination with ABO and Rh typing. HLA testing has been used for about five years in paternity cases in Europe, and recently a joint committee of the American Medical Association and the American Bar Association studying serologic tests for paternity evaluation recommended "widespread inclusion of HLA studies in the battery of tests used in cases of disputed paternity."

HLA is the major histocompatibility system in man, and has an extreme diversity of antigens in several closely linked serologically detectable genetic loci. At present, the practical use of HLA in paternity cases is confined to typing of two loci, HLA-A and HLA-B. The system is one of codominant genes, so two antigens may be present for each locus. The World Health Organization Leukocyte Nomenclature Committee recognizes a total of 39 separate specificities for the A and B loci. A tissue typing laboratory that can detect most or all of these specificities can type for about 300 haplotypes with as many as 100,000 genotypes.

In cases of nonexclusion of a putative father, an estimate of the likelihood of paternity is desirable in utilizing the serologic results. In "one-man" cases, generally a computation is used that compares the nonexcluded putative father with a random male in the population. In our laboratory, formulas have been derived to utilize population haplotype frequencies rather than simple gene frequencies, since haplotypes generally are inherited as a unit and genetic disequilibrium is known to exist between antigens of HLA-A and HLA-B. This computation does not assume probable haplotypes, but takes into account all possibilities for each person as well as considering recombination frequencies. In our experience with over 1,000 disputed paternity cases, nearly 90 percent of the nonexcluded cases had probability of paternity greater than 90 percent. Undoubtedly, utilization of HLA typing in paternity cases in the United States will continue to increase rapidly as education about the extreme usefulness of such tests becomes more widespread and legislation is altered accordingly.

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Pacemaker Postmortem

THE CARDIAC PACEMAKER stands in the forefront of the bionic age. Thousands of people now live and eventually will die with a complex electrical pulse generator functioning inside their bodies. This generator provides a substitute electrical impulse for the heart's completely or incompletely blocked electrical system. In death, the question sometimes arises whether a pacemaker malfunction or complication contributed in any way.

The pathologist, therefore, should examine the pacemaker and its lead as an integral part of an autopsy. He or she always should ask: (1) Was there a signal? (2) Was it effective? (3) Could anything have altered it?

The generator should be tested electronically for rate, pulse amplitude, pulse width and R-wave

inhibition. Any hospital where pacemakers are implanted should have a device that can test for these. The lead should be inspected *in situ* before removal to make sure it is in the proper location and is providing a proper myocardial contact. Testing at the lead terminal will establish its continuity with the generator.

The history is important to determine if some outside electrical exposure such as electrocautery could have affected the unit.

The presence of the pacemaker as a foreign body can complicate matters. The implant site can become infected and the infection may migrate down the lead into the circulatory system. Thrombi may form about the lead and provide a source of emboli.

Testing of cardiac pacemakers postmortem not only aids in determining the cause of death but also, on a larger scale, helps prevent other deaths by monitoring for product defects. These should be reported to the Bureau of Medical Devices, Food and Drug Administration.

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Platelet Function Testing

PLATELETS occupy a key role in maintaining vascular integrity and initiating the clotting process. In recent years increasing interest has developed in testing quantitative as well as functional variations of platelets.

Although the reference method for platelet counting is phase microscopy, a number of reliable automatic counting devices are available. Only rarely is a factitious result produced by cold agglutinins, platelet satellitosis or giant forms of platelets.

The bleeding time is the classic measure of platelet effectiveness because it is sensitive both to quantitative and qualitative alterations.

The Ivy bleeding time test is done by inflating a sphygmomanometer cuff to 40 mm of mercury, making an incision lower on the arm and determining the duration of bleeding (normal 2½ to 10 minutes). Standardization of this procedure has been improved with a template which controls the length and depth of incision. Times are prolonged in thrombocytopenia, usually in von Willebrand disease and often in normal subjects taking aspirin.

Platelet retention testing involves passing blood through a column containing glass beads. Normally 80 percent of platelets are retained in the filter bed. This test is more sensitive than the bleeding time test but subject to many variables. It would be more useful if a standardized commercially available kit allowed greater interlaboratory comparison.

Clot retraction measurements are semiquantitative appraisals of platelet function. Retraction is deficient in thrombocytopenia and in a rare autosomal recessive disorder, Glanzmann thrombasthenia. Careful laboratory control is important.

Platelet aggregometry is done by passing a beam of light through a suspension of citrated platelet rich plasma. On addition of appropriate reagents an aggregate forms, causing a change of light transmission. Adenosine diphosphate (ADP) can aggregate platelets directly. Epinephrine and collagen produce a biphasic curve of aggregation by inducing platelet secretion and release of endogenous ADP.

A series of defects in primary and secondary aggregation has been noted in patients with bleeding disorders. Patients with von Willebrand disease show impaired, ristocetin-induced platelet aggregation. In thrombasthenia, platelets do not aggregate when exposed to ADP. The best known acquired functional alteration is that produced by aspirin. Since many aspirin derivatives and other drugs affect platelet aggregation, all medication should be avoided for ten days before the test is done. With platelet counts below 50,000 results of aggregometry are unreliable.

A dialysable substance present in the blood of uremic patients interferes with platelet aggregation. In a patient with cirrhosis there also may be defective platelet function.

Tests of platelet functions are influenced by many variables and can be capricious. Thus laboratory standardization of equipment, sampling technique and normal controls is particularly important.

Platelet aggregometry is sensitive to so many agents that it seems prudent to show an observed abnormality on more than one occasion before assigning it a causal role in a patient with a bleeding history. Additional clinical experience